(2) Scientific Abstract

Squamous cell carcinomas of the head and neck (SCCHN), unlike normal mucosal squamous epithelial cells, overexpress epidermal growth factor receptor (EGFR) mRNA and protein. EGFR protein is required to sustain the proliferation of SCCHN cells *in vitro*. To determine whether EGFR expression contributes to tumor growth, we previously demonstrated suppression of EGFR expression in tumor xenografts and inhibition of tumor growth following intratumoral administration of an antisense EGFR expression plasmid. The original U6 expression construct (pGEMmU6) was modified to introduce Xho I and Nsi I sites for convenient cloning and a 5′ hairpin loop responsible for capping of the U6 RNA was eliminated using PCR-mediated deletion. A 39 base pair antisense oligonucleotide corresponding to the ATG start site of the human EGFR gene (-20 to +20) was synthesized and cloned into the Xho I and Nsi I sites of the new plasmid. Direct inoculation of this EGFR antisense construct into established SCCHN xenografts resulted in inhibition of tumor growth, suppression of EGFR expression and increased apoptosis. Sustained effects were observed for up to one year after treatments were discontinued. Toxicity studies revealed no evidence of organ damage. The plasmid backbone was subsequently replaced with a previously approved vector for use in clinical trials (pNGVL1). The CMV promoter sequences were removed to eliminate the possibility of interference with the U6 promoter. Although the original investigations utilized cationic lipids, subsequent studies demonstrated that the lipid carrier was not required for antitumor efficacy. Intratumoral or intravenous administration of this plasmid (naked DNA) in head and neck cancer xenografts was growth inhibitory. In DNA distribution studies, the EGFR antisense DNA was detected in several organs, including the injection site for up to 2 days after a single treatment. This phase I clinical trial is designed to determine whether interference with EGFR expression, using an intratumoral antisense-based gene therapy approach may be a safe and effective means of treating EGFR-overexpressing tumors, including SCCHN.